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Risk comparison for prenatal use of analgesics and selected birth defects, National Birth Defects Prevention Study 1997–2011

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Abstract

Purpose—To compare the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or opioids to the use of acetaminophen without NSAIDs or opioids with respect to associations with birth defects.

Methods—We used data from the National Birth Defects Prevention Study (1997–2011). Exposure was self-reported maternal analgesic use from the month before through the third month of pregnancy (periconceptional). Adjusted odds ratios (aORs) were calculated to examine associations with 16 birth defects.

Results—Compared to acetaminophen, mothers reporting NSAIDs were significantly more likely to have offspring with gastroschisis, hypospadias, cleft palate, cleft lip with cleft palate, cleft lip without cleft palate, anencephaly, spina bifida, hypoplastic left heart syndrome, pulmonary valve stenosis, and tetralogy of Fallot (aOR range, 1.2–1.6). Opioids were associated with

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tetralogy of Fallot, perimembranous ventricular septal defect, and ventricular septal defect with atrial septal defect (aOR range, 1.8–2.3), whereas use of both opioids and NSAIDs was associated with gastroschisis, cleft palate, spina bifida, hypoplastic left heart syndrome, and pulmonary valve stenosis (aOR range, 2.0–2.9).

Conclusions—Compared to periconceptional use of acetaminophen, selected birth defects occurred more frequently among infants of women using NSAIDs and/or opioids. However, we could not definitely determine whether these risks relate to the drugs or to indications for treatment.

Keywords

Congenital abnormalities; Pregnancy; Teratogens; Analgesics; Analgesics; Opioids; Acetaminophen; Anti-inflammatory agents; Nonsteroidal

Introduction

Chronic and acute nonobstetric pain during pregnancy is common and can arise from prepregnancy maternal conditions such as sickle cell disease, arthritis, headache, injury, and surgery (collectively affecting up to 25% of pregnant women [1–5]), as well as pregnancy-related conditions such as lower back pain and pelvic pain (together affecting 22%–72% of pregnant women [6,7]). The selection of safe and effective pain management strategies during pregnancy is challenging [8,9]. Early embryonic exposure to certain pain medications can result in potentially harmful effects on the fetus [9,10]. Alternatively, fear about the use of drugs during pregnancy, both substantiated and unfounded, can lead to undertreatment of pregnant women for painful conditions; comorbidities due to inadequate pain management can also be harmful to the fetus [8,9,11,12].

Analgesic use during pregnancy is estimated to range from approximately 50% to 80% [13,14], with the majority of use occurring during the first trimester, which is of particular concern due to potential teratogenic risk during the period of organogenesis [15]. Some of the most commonly used analgesics for pain management in the first trimester include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids (reported first trimester use in 41%–59% [14,16], 8%–24% [14,17,18], 2%–11% [19,20], respectively). Previous studies have examined teratogenic effects of analgesic use during the first trimester, and while acetaminophen is generally considered safe in regard to teratogenicity, findings for NSAIDs and opioids have been inconsistent [9,11,12,21].

Research is needed to comparatively assess the safety of these analgesics to help guide the treatment of pain in pregnancy [9,22]. The objectives of our study were (1) to document the prevalence and patterns of self-reported use of acetaminophen, NSAIDs, and opioids during pregnancy and (2) to compare the use of early pregnancy NSAIDs and/or opioids to acetaminophen with respect to associations with selected birth defects.

Materials and methods

The National Birth Defects Prevention Study (NBDPS) was a population-based, multisite, case-control study of more than 30 major structural birth defects across 10 centers in the United States (Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas, and Utah). Birth defect cases, including live born, stillborn, and induced abortions, were identified by each Center's birth defects registry, excluding cases with a known cause (e.g., chromosomal or genetic disorders). Live-born controls were randomly selected from birth certificates or birth hospitals in the same region and month of birth as cases. The specifics of study selection and case classification have been detailed in previous publications [23,24].

Eligible cases and controls were interviewed in English or Spanish from 6 weeks to 24 months after the estimated date of delivery (EDD), with participation of 67% among cases and 65% among controls. Before the interview, participants were mailed pregnancy calendars to assist in accurate reporting of medication use timing. Mothers were asked about conditions such as diabetes, high blood pressure, seizures, respiratory illnesses, infections, fevers, chronic diseases, injuries, and surgeries from 3 months before conception (B3) through the end of pregnancy (P9). In each of those questionnaire sections, mothers were asked about medications they took for treatment of those conditions; in addition, they were encouraged to report any additional prescription or nonprescription medications. All medications reported were compiled and coded using the Slone Drug Dictionary, which links drug products to their active ingredients [25]. Informed consent was obtained from all participants, and all protocols, materials, and interview content were approved by the Centers for Disease Control and Prevention and local Institutional Review Boards for each center.

To best address the two objectives of the study, we used different gestational periods of exposure for analyses of patterns of analgesic use (descriptive analysis) and analyses for estimating odds ratios (comparative analysis). For the descriptive analysis, we defined analgesic use in pregnancy as the use of acetaminophen, NSAIDs, or opioids in B3–P9. In our comparative analysis, we defined periconceptional analgesic use as use from 1 month before conception (B1) through the third month of pregnancy (P3). Because many over-the-counter analgesics are predominantly available in combination with other medications [26], all exposure groups included individual analgesic products and products in combination with nonanalgesics. Because many women used both NSAIDs and acetaminophen and because many opioid products include acetaminophen [8,15,27], we created mutually exclusive categories of exposure: (1) NSAIDs without opioids (with or without acetaminophen); (2) opioids without NSAIDs (with or without acetaminophen); (3) both opioids and NSAIDs (with or without acetaminophen); and (4) acetaminophen (without NSAIDs or opioids). As a subanalysis, we further stratified the exposures into mutually exclusive groups based on the most commonly reported specific medications: NSAIDs into ibuprofen, aspirin, and naproxen; and opioids into hydrocodone and codeine.

In all analyses, we excluded mothers with pregestational diabetes, self-reported heroin or opioid abuse in B3–P9, missing medication information or dates of use, or who had used a

known teratogen (i.e., misoprostol, methotrexate, mycophenolate mofetil, thalidomide, isotretinoin, warfarin, or valproic acid [28]) in B3–P9. In comparative analyses, we additionally excluded mothers who did not use an analgesic periconceptionally, did not report analgesic type, or reported analgesic use "as needed" in B3–P9 without specifying timing. We analyzed cases and controls with pregnancies ending on or after October 1, 1997, to EDDs on or before December 31, 2011. Potential covariates were identified *a priori* and included maternal age at delivery (continuous; <20 years, 20–34 years, ≥ 35 years), race/ethnicity (non-Hispanic white, other), prepregnancy body mass index (≥30 kg per m^2, <30 kg per m^2), previous live birth (≥1, 0), maternal education (<12 years, ≥12 years), study location, EDD year (1997–2001, 2002–2006, 2007–2011), and the following dichotomous variables: folic acid consumption B1 through the first month of pregnancy (P1), periconceptional alcohol, smoking, and antibiotic use (to better account for analgesic use as a result of a possible infection), and infant sex. We used χ^2, Fisher's exact, and two-sample *t*-tests to assess whether these factors varied significantly by analgesic exposure among mothers of control infants.

We used logistic regression to estimate crude and adjusted odds ratios and 95% confidence intervals for the association between birth defects and use of NSAIDs, opioids, and both opioids and NSAIDs, compared to acetaminophen use. Acetaminophen was selected for comparison due to previous assessments of its general safety in the first trimester in relation to birth defects [16] and from exploratory analyses using this study's data (Supplemental Table 1). Covariates with significant associations with analgesic exposures were included in the adjusted model. As this study builds on previous work using the same data source, birth defects of interest were selected based on positive associations with one or more of the analgesics of interest noted in previous studies [10,14,18,19,22,26,29–32]. Statistical significance was set at $P < .05$, and all analyses were conducted using SAS 9.3 (Cary, NC).

We conducted a number of sensitivity analyses based on excluding certain groups from the main comparative analysis, including (1) periconceptional surgery, (2) injury, or (3) fever; (4) selected chronic conditions; (5) a family history of birth defects in a first degree relative; and (6) periconceptional use of selected common nonanalgesics. Furthermore, we (7) limited outcomes to isolated cases (with only one major defect diagnosed), (8) limited analyses to women reporting wanting to become pregnant, and (9) restricted to mothers with 6 (minimum) to 42 (median) weeks between EDD and interview to address potential recall bias. In addition, because of the increasing prevalence of gastroschisis [33], especially among younger (<20 years) mothers, we assessed whether there was interaction between maternal age at delivery (<20, assessed whether there was interaction between maternal age at delivery (<20, ≥20 years) with analgesic exposure and gastroschisis in offspring. Moreover, to better understand the differences between the opioid exposure group and the both opioids and NSAIDs exposure group, we explored whether there were differences in reporting by questionnaire section in which opioids were reported.

Results

Descriptive analysis

Among 29,078 case and 10,962 control mothers meeting our initial inclusion criteria for the descriptive analysis, 81% of cases and 80% of controls reported analgesic use in B3–P9, with 57% of cases and 54% of controls reporting periconceptional analgesic use (Figs. 1 and 2). Acetaminophen use increased slightly from B1–P1 and decreased before delivery (ranging in B3–P9 between 42% and 47% among cases and 39% and 46% among controls). NSAID use was highest during the 3 months before pregnancy and decreased drastically from B1–P3 (dropping from 30% to 11% among cases and 24% to 10% among controls). Opioid use was consistent throughout pregnancy (at 1% in B3–P9 for both cases and controls). Most mothers reporting acetaminophen did so as their only analgesic (58%), whereas most mothers reporting NSAID, opioids, or both also reported using acetaminophen (70%, 45%, and 46%, respectively) (Supplemental Table 2).

Comparative analysis

Based on positive associations observed in previous literature [10,14,18,19,22,26,29–32], 16 birth defect case groups of interest were identified and included in our comparative analysis, involving 9179 case and 5944 control mothers who reported analgesics periconceptionally. The exposed and comparison groups for analyses were made up of 48% of case (54% of control) mothers reporting acetaminophen, 48% (42%) NSAIDs, 2% (2%) opioids, and 2% (1%) both opioids and NSAIDs. Among mothers who used NSAIDs, 71% (72%) reported ibuprofen, 9% (9%) reported aspirin, and 6% (7%) reported naproxen. Among mothers who used opioids, 38% (26%) reported hydrocodone and 29% (27%) reported codeine.

Compared to control mothers who reported acetaminophen use, those reporting NSAID use were significantly more likely to be older at delivery, non-Hispanic white, nulliparous, high school graduates, report periconceptional alcohol and smoking, have a different study location, and have a later EDD year; those who reported opioid use were significantly more likely to be non-Hispanic white, report periconceptional smoking and antibiotic use, and have a later EDD year; and those who reported both opioids and NSAIDs were significantly more likely to be older at delivery, non-Hispanic white, high school graduates and report periconceptional smoking and antibiotic use (Table 1).

Compared to mothers who reported acetaminophen use, use of NSAIDs was significantly associated with seven non-heart and three heart defects in the offspring: gastroschisis, hypospadias, orofacial clefts, anencephaly and craniorachischisis, spina bifida, hypoplastic left heart syndrome, pulmonary valve stenosis (PVS), and tetralogy of Fallot (TOF) (Table 2), with the highest risks for gastroschisis and spina bifida. The use of ibuprofen was associated with the same set of birth defects as the larger NSAID exposure group, except for cleft lip without cleft palate, which was associated with the use of aspirin (Table 3). Use of opioids was significantly associated with three heart defects: TOF, perimembranous ventricular septal defect (VSD), and VSD with atrial septal defect (ASD) (Table 2). The use of hydrocodone was associated with a similar set of heart defects, with the exclusion of VSD with atrial septal defect, and with two non-heart defects: cleft palate and cleft lip with cleft

palate. Codeine was associated with perimembranous VSD (Table 4). Periconceptional use of both opioids and NSAIDs was associated with three non-heart defects and two heart defects: gastroschisis, cleft palate, spina bifida, and hypoplastic left heart syndrome and PVS, respectively (Table 2).

In the sensitivity analyses where we excluded certain groups, the associations between NSAIDs and many selected birth defects remained fairly consistent (Supplemental Figure). However, a few slight changes were found in sensitivity analyses involving opioids, in which removing periconceptional surgery, fever, or nonanalgesic medication use led to increased risks for some birth defects. In the sensitivity analysis of gastroschisis, we found no evidence of an interaction between analgesic exposures and maternal age (data not shown). The most common questionnaire sections in which opioid use was reported related to procedures (23% each) and injuries (11% each), with a moderate portion “not specified” (37% and 41%, respectively) (data not shown). However, for those with a section specified (i.e., proxy for reason for analgesic use), there were no notable differences between mothers reporting opioids and those reporting both opioids and NSAIDs.

Conclusions

In this analysis, we found that approximately 80% of women reported analgesic use in pregnancy, with approximately 50%–60% reporting use periconceptionally. In addition, we found that compared to periconceptional use of acetaminophen, selected birth defects, both non-heart and heart, occurred more frequently among women reporting use of NSAIDs. The occurrence of selected birth defects was even higher among women reporting use of opioids. However, those associations were generally confined to selected heart defects among women reporting any opioid use, whereas the association with some non-heart defects was only seen among women reporting use of hydrocodone specifically. The associations we observed between opioids and birth defects persisted even when we removed individuals with surgery, fever, or use of other nonanalgesic medications, providing further support that these associations are more likely due to opioid medication use than the indications for use. The greatest occurrence of selected birth defects was among women reporting use of both opioids and NSAIDs. Although this finding could be due to an additive effect of the use of opioids and NSAIDs concurrently or due to increased analgesic exposure overall, the cause for this difference is unclear from our analyses and data available. However, it is unlikely that this difference is due to an increased severity of underlying illness among women reporting use of both opioids and NSAIDs as our findings did not vary greatly across the sensitivity analyses conducted.

No other studies that we are aware of have compared the use of analgesic medications to each other with respect to birth defect associations. Because many women need treatment for pain in pregnancy, this comparison of different pain management strategies is warranted. Comparing our study to previous literature is difficult because most studies that examined analgesic use in early pregnancy used an unexposed comparator, and many studies used the same data source and overlapping study population as this study, including Hernandez et al. [18], Lind et al. [32], Cleves et al. [17], and Broussard et al. [19]. However, these studies using the same data source analyzed data with EDDs up to 2007 while our study analyzed

data through 2011, adding 28% more cases and controls. In previous NBDPS analyses of NSAIDs, Hernandez et al. [18] found aspirin associated with anencephaly and cleft palate, ibuprofen with spina bifida and cleft lip with/without cleft palate, and naproxen with cleft lip with/without cleft palate; and Lind et al.'s [32] NBDPS analysis found ibuprofen associated with hypospadias. In this study, we also found associations between ibuprofen and spina bifida, cleft lip with cleft palate, and hypospadias. Cleves et al.'s [17] NBDPS study of muscular VSDs found no associations with first-trimester NSAID use (with or without the use of acetaminophen), similar to our negative finding. Broussard and colleagues' [19] analyses of opioid use in NBDPS found significant associations with gastroschisis, any neural tube defect, spina bifida, PVS, and TOF. These results did not correspond to our findings for opioid use without NSAIDs, but rather with our findings for use of both opioids and NSAIDs, a distinction not made in their study.

In non-NBDPS studies, a few additional data sources have shown associations between NSAIDs and birth defects. In a Swedish cohort study, Ericson and Kallen [34] found early pregnancy naproxen use associated with orofacial clefts. In addition, a few studies found associations between aspirin and gastroschisis, including Werler et al. [26] using case-control data from 15 cities across the United States and Canada, Torfs et al. [35] using data from the California Birth Defects Monitoring Program, and Drongowski et al. [36]. Our study did not find any associations between naproxen and selected birth defects and only saw a significant association between aspirin and cleft lip without cleft palate, which did not match findings from the previously mentioned studies. However, the naproxen association found by Ericson and Kallen [34] was based on only five exposed cases (compared to our 81). The studies that found the aspirin association had various limitations. Werler et al. [26] was based on 13 exposed cases (compared to our 34), with a comparison group that included both malformed and nonmalformed controls, whereas Torfs et al. [35] was based on only seven exposed cases and Drongowski et al.'s [36] results were tentative because of high nonresponse and an unexpectedly high proportion of aspirin users in the case group. Using data from the Slone Epidemiology Center Birth Defects Study, Yadzy et al. [30] examined periconceptional opioid use, but the concomitant use of NSAIDs was not examined. Significant associations were found with gastroschisis, any neural tube defect, spina bifida, PVS, and TOF, which, as with the Broussard et al. [19] study, only correspond to our findings for use of both opioids and NSAIDs. Using data from the Baltimore–Washington Infant Study, Marsh et al.'s [14] study is the only other study that we are aware of that examined all three analgesics (acetaminophen, NSAIDs, and opioids) but, like other studies, used an unexposed comparator and only examined cardiovascular malformations. Marsh et al. [14] found non-salicylate NSAIDs associated with dextro-Transposition of the great arteries with intact ventricular septum, a category of heart defects that we were not able to examine. However, they did not find an association with dextro-Transposition of the great arteries in general, matching the findings of our study.

While this analysis utilized the largest U.S. population-based study of birth defects, with the ability to assess individual analgesics and individual birth defects, the study is subject to several important limitations. First, we lacked information on specific indication. While use of an active comparator attempted to reduce confounding by indication, as did our exclusion of specific groups in multiple sensitivity analyses, analgesics included in the analysis are

used for a variety of indications (pain, fever, inflammation, etc.) for which we were unable to completely account. Women may have been channeled by their physician to acetaminophen for more benign conditions given its perceived safety profile during pregnancy, whereas women taking NSAIDs and opioids may have had more serious or complex conditions or symptoms for which the benefit of these medications was perceived by the prescriber to outweigh any risks. Second, because analgesics are often used in combination with other analgesic and nonanalgesic medications, the effects of individual medications are hard to differentiate. Third, because exposure information was self-reported and could have occurred up to two years before interviews, recall is subject to misclassification. However, multiple questions were asked to determine medication use, and the self-reported nature provides information on actual consumption rather than prescription alone. Fourth, we were not able to assess dose or whether women took these medications during the critical time period relative to the defect of interest. Conversely, the long exposure risk window may lend itself to a dilution of potential teratogenic risk. Fifth, the analytic design of our study does not lend itself to assessment of risks associated with acetaminophen because we used it as the comparator; however, we did not see any effects of acetaminophen itself when compared to unexposed women using these data (Supplemental Table 1). Finally, because we conducted almost 600 statistical tests, we would expect approximately 30 statistically significant results due to chance alone. However, we would not expect this random error to explain the disproportionate increased risks of heart-related defects observed primarily in opioid users.

In conclusion, we found that compared to periconceptional use of acetaminophen, selected birth defects occurred more frequently among women reporting use of NSAIDs and/or opioids. However, while many of the selected birth defects were associated with the use of NSAIDs, risks were small with a 1.5-fold increase, and while the use of both opioids and NSAIDs had a two- to three-fold increased risk for both non-heart and heart defects, these results translate to a modest increase in absolute risk. Moreover, it is unclear whether these increased associations are attributable to NSAIDs and/or opioids or to the indications for which these medications were taken. Pain management in pregnancy is important for the health of both the mother and fetus, and any pain management strategy considerations should weigh the risks and benefits for patients who are or may be pregnant. Future research should continue to compare the relative fetal safety of individual analgesics within these classes to help guide clinicians in the selection of safe and effective pain management strategies in pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of the U.S. Centers for Disease Control and Prevention or the Food and Drug Administration.

References

1. Boulet SL, Okoroh EM, Azonobi I, Grant A, Craig Hooper W. Sickle cell disease in pregnancy: maternal complications in a Medicaid-enrolled population. Matern Child Health J. 2013; 17:200–7. [PubMed: 23315242]
2. Choi HJ, Lee JC, Lee YJ, Lee EB, Shim SS, Park JS, et al. Prevalence and clinical features of arthralgia/arthritis in healthy pregnant women. Rheumatol Int. 2008; 28:1111–5. [PubMed: 18548252]
3. Erdogan FF, Ozturk A, Unalan D, Mazicioglu M, Serin IS, Tucer B. Prevalence of and influencing factors for chronic headaches among pregnant women. Int J Gynaecol Obstet. 2012; 117:144–7. [PubMed: 22365591]
4. Tinker SC, Reefhuis J, Dellinger AM, Jamieson DJ. Maternal injuries during the periconceptional period and the risk of birth defects, National Birth Defects Prevention Study, 1997–2005. Paediatr Perinat Epidemiol. 2011; 25:487–96. [PubMed: 21819430]
5. Kuczkowski KM. Nonobstetric surgery during pregnancy: what are the risks of anesthesia? Obstet Gynecol Surv. 2004; 59:52–6. [PubMed: 14707749]
6. Mogren IM, Pohjanen AI. Low back pain and pelvic pain during pregnancy: prevalence and risk factors. Spine. 2005; 30:983–91. [PubMed: 15834344]
7. Ostgaard HC, Andersson GB, Karlsson K. Prevalence of back pain in pregnancy. Spine. 1991; 16:549–52. [PubMed: 1828912]
8. Pritham UA, Mckay L. Safe management of chronic pain in pregnancy in an era of opioid misuse and abuse. J Obstet Gynecol Neonatal Nurs. 2014; 43:554–67.
9. Coluzzi F, Valensise H, Sacco M, Allegri M. Chronic pain management in pregnancy and lactation. Minerva Anestesiol. 2014; 80:211–24. [PubMed: 23857445]
10. Wunsch MJ, Stanard V, Schnoll SH. Treatment of pain in pregnancy. Clin J Pain. 2003; 19:148–55. [PubMed: 12792553]
11. Kennedy D. Analgesics and pain relief in pregnancy and breastfeeding. Aust Presc. 2011; 34:e441–7.
12. Babb M, Koren G, Einarson A. Treating pain during pregnancy. Can Fam Physician. 2010; 56:25–7. [PubMed: 20090076]
13. Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. Am J Obstet Gynecol. 2005; 193:771–7. [PubMed: 16150273]
14. Marsh CA, Cragan JD, Alverson CJ, Correa A. Case-control analysis of maternal prenatal analgesic use and cardiovascular malformations: Baltimore-Washington Infant Study. Am J Obstet Gynecol. 2014; 211:404.e1–9. [PubMed: 24681289]
15. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernandez-Diaz S. Medication use during pregnancy, with particular focus on prescription drugs: 1976–2008. Am J Obstet Gynecol. 2011; 205:51.e1–8. [PubMed: 21514558]
16. Feldkamp ML, Meyer RE, Krikov S, Botto LD. Acetaminophen use in pregnancy and risk of birth defects: findings from the National Birth Defects Prevention Study. Obstet Gynecol. 2010; 115:109–15. [PubMed: 20027042]
17. Cleves MA, Savell VH Jr, Raj S, Zhao W, Correa A, Werler MM, et al. Maternal use of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), and muscular ventricular septal defects. Birth Defects Res A Clin Mol Teratol. 2004; 70:107–13. [PubMed: 15039924]

18. Hernandez RK, Werler MM, Romitti P, Sun L, Anderka M. Nonsteroidal antiinflammatory drug use among women and the risk of birth defects. Am J Obstet Gynecol. 2012; 206:228.e1–8. [PubMed: 22196851]
19. Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, et al. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol. 2011; 204:314.e1–314.e11. [PubMed: 21345403]
20. Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. Obstet Gynecol. 2014; 123:997–1002. [PubMed: 24785852]
21. Yazdy MM, Desai RJ, Brogly SB. Prescription opioids in pregnancy and birth outcomes: a review of the literature. J Pediatr Genet. 2015; 4:56–70. [PubMed: 26998394]
22. Adams K, Bombardier C, Van Der Heijde DM. Safety of pain therapy during pregnancy and lactation in patients with inflammatory arthritis: a systematic literature review. J Rheumatol Suppl. 2012; 90:59–61. [PubMed: 22942331]
23. Reefhuis J, Gilboa SM, Anderka M, Browne ML, Feldkamp ML, Hobbs CA, et al. The National Birth Defects Prevention Study: a review of the methods. Birth Defects Res A Clin Mol Teratol. 2015; 103:656–69. [PubMed: 26033852]
24. Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SL, et al. The National Birth Defects Prevention Study. Public Health Rep. 2001; 116(Suppl 1):32–40.
25. Kelly K, Kelley T, Kaufman D, Mitchell A. The Slone drug dictionary: a research-driven pharmacoepidemiology tool. Pharmacoepidemiol Drug Saf. 2003; 12:S168–9.
26. Werler MM, Sheehan JE, Mitchell AA. Maternal medication use and risks of gastroschisis and small intestinal atresia. Am J Epidemiol. 2002; 155:26–31. [PubMed: 11772781]
27. Nezvalova-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: results from a large population-based cohort study. Eur J Clin Pharmacol. 2011; 67:1253–61. [PubMed: 21656212]
28. Obican S, Scialli AR. Teratogenic exposures. Am J Med Genet C Semin Med Genet. 2011; 157c: 150–69. [PubMed: 21766437]
29. Browne ML, Van Zutphen AR, Botto LD, Louik C, Richardson S, Druschel CM. Maternal butalbital use and selected defects in the National Birth Defects Prevention Study. Headache. 2014; 54:54–66. [PubMed: 24001268]
30. Yazdy MM, Mitchell AA, Tinker SC, Parker SE, Werler MM. Periconceptional use of opioids and the risk of neural tube defects. Obstet Gynecol. 2013; 122:838–44. [PubMed: 24084542]
31. Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, et al. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young. Circulation. 2007; 115:2995–3014. [PubMed: 17519397]
32. Lind JN, Tinker SC, Broussard CS, Reefhuis J, Carmichael SL, Honein MA, et al. Maternal medication and herbal use and risk for hypospadias: data from the National Birth Defects Prevention Study, 1997–2007. Pharmacoepidemiol Drug Saf. 2013; 22:783–93. [PubMed: 23620412]
33. Jones AM, Isenburg J, Salemi JL, Arnold KE, Mai CT, Aggarwal D, et al. Increasing Prevalence of Gastroschisis - 14 States, 1995–2012. MMWR Morb Mortal Wkly Rep. 2016; 65:23–6. [PubMed: 26796490]
34. Ericson A, Kallen BA. Nonsteroidal anti-inflammatory drugs in early pregnancy. Reprod Toxicol. 2001; 15:371–5. [PubMed: 11489592]
35. Torfs CP, Katz EA, Bateson TF, Lam PK, Curry CJR. Maternal medications and environmental exposures as risk factors for gastroschisis. Teratology. 1996; 54:84–92. [PubMed: 8948544]
36. Drongowski RA, Smith RK, Coran AG, Klein MD. Contributions of demographic and environmental factors to the etiology of gastroschisis: a hypothesis. Fetal Diagn Ther. 1991; 6:14–27. [PubMed: 1837456]

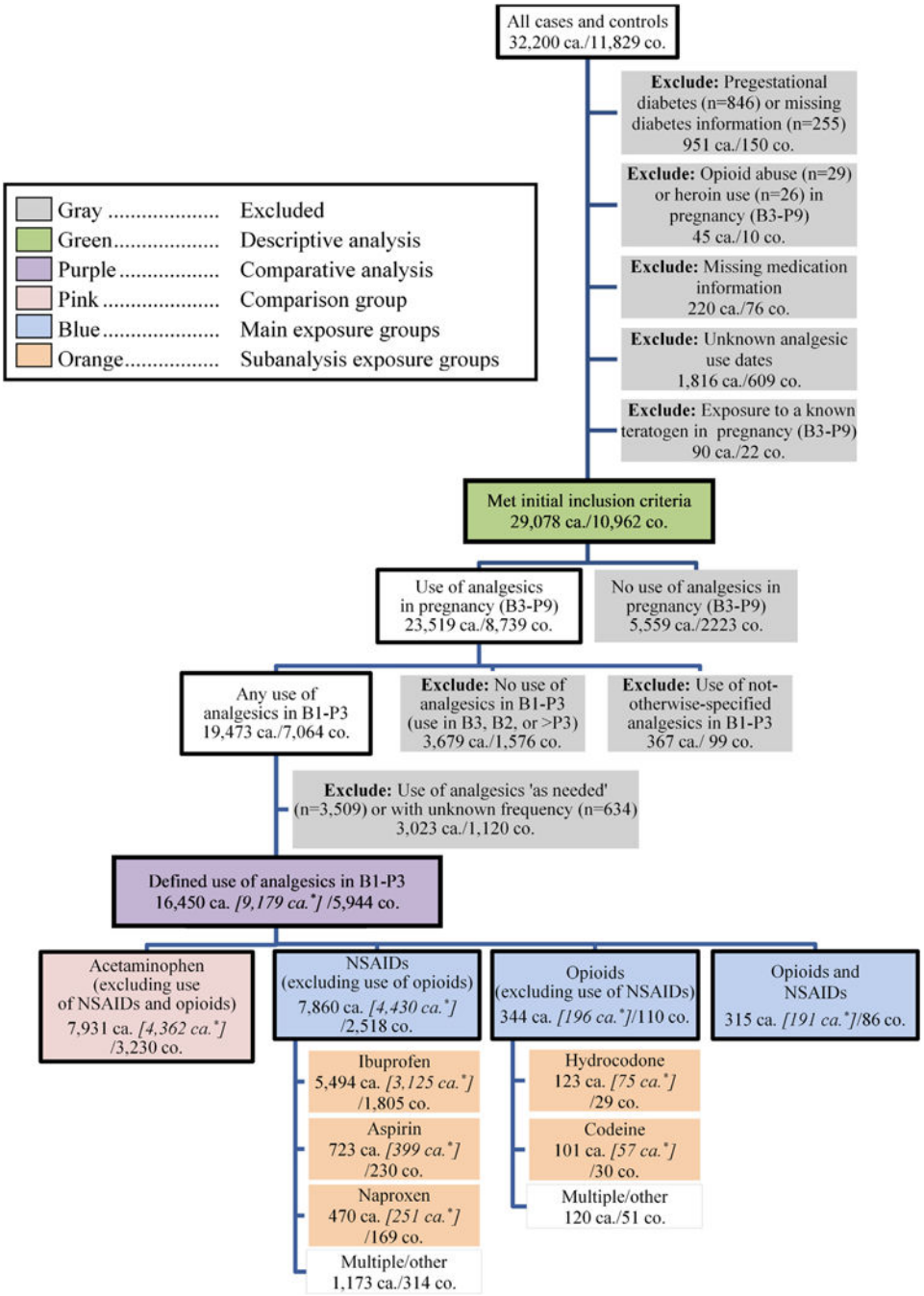

Fig. 1.

Study selection flowchart, National Birth Defects Prevention Study 1997–2011. Flowchart showing exclusion criteria leading to final sample size included in this analysis. Ca. = cases; Co. = controls; B3–P9 = 3 months before conception through the end of pregnancy; B1–P3 = 1 month before conception through third month of pregnancy; NSAIDs = nonsteroidal anti-inflammatory drugs; *After restricting to defects with positive associations with one or more of the analgesics of interest noted in previous studies.

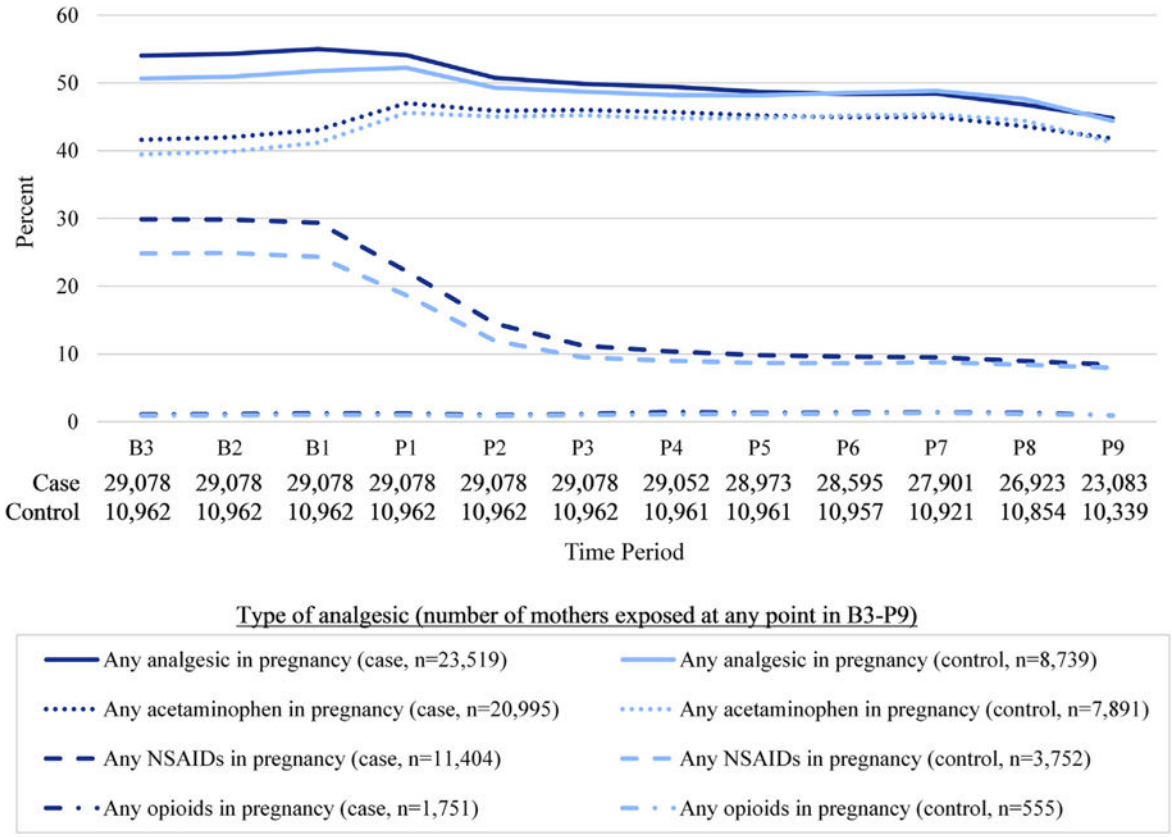

Fig. 2.

Proportion of mothers reporting analgesic use, among mothers meeting initial inclusion criteria, from B3–P9, National Birth Defects Prevention Study 1997–2011. Line graph showing the proportion of mothers using specific analgesics by month of use among mothers who reported any use from 3 months before conception (B3) through the end of pregnancy (P9). Analgesic categories are not mutually exclusive.

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Table 1

Study population characteristics among mothers of controls included in comparative analysis, National Birth Defects Prevention Study 1997–2011 (*n* = 5944)

Characteristic	Acetaminophen* (*n* = 3230)	NSAIDs* (*n* = 2518)		Opioids* (*n* = 110)		Opioids and NSAIDs* (*n* = 86)	
	n (%)	*n* (%)	*P*†	*n* (%)	*P*†	*n* (%)	*P*†
Maternal age at delivery, years							
Mean ± standard deviation	27.7 ± 5.9	28.2 ± 6.1	<.01	27.7 ± 5.4	.96	29.5 ± 6.1	.01
<20	391 (12.1)	310 (12.3)	.07	10 (9.1)	.18	7 (8.1)	.29
20–34	2391 (74.0)	1806 (71.7)		90 (81.8)		63 (73.3)	
≥35	448 (13.9)	402 (16.0)		41 (9.1)		16 (18.6)	
Maternal race/ethnicity							
Non-Hispanic white	2072 (64.2)	1712 (68.0)	<.01	81 (73.6)	.04	71 (82.6)	<.01
Other	1156 (35.8)	805 (32.0)		29 (26.4)		15 (17.4)	
Unknown	2 (0.1)	1 (0.0)		0 (0.0)		0 (0.0)	
Maternal prepregnancy BMI							
Obese (≥30 kg/m^2)	609 (18.9)	437 (17.4)	.11	27 (24.6)	.18	16 (18.6)	.85
Not (<30 kg/m^2)	2528 (78.3)	2027 (80.5)		83 (75.5)		70 (81.4)	
Unknown	93 (2.9)	54 (2.1)		0 (0.0)		0 (0.0)	
Number of previous live births							
None	1189 (36.8)	1162 (46.2)	<.01	36 (32.7)	.38	23 (26.7)	.06
One or more	2039 (63.1)	1356 (53.9)		74 (67.3)		63 (73.3)	
Unknown	2 (0.1)	0 (0.0)		0 (0.0)		0 (0.0)	
Maternal education							
<High school	450 (13.9)	306 (12.2)	.04	13 (11.8)	.58	3 (3.5)	.01
≥High school	2724 (84.3)	2177 (86.5)		93 (85.6)		80 (93.0)	
Unknown	56 (1.7)	35 (1.4)		4 (3.6)		3 (3.5)	
Maternal folic acid consumption‡							
Yes	1775 (55.0)	1428 (56.7)	.20	70 (63.6)	.08	50 (58.1)	.51
No	1440 (44.6)	1081 (43.9)		40 (36.4)		35 (40.7)	
Unknown	15 (0.5)	9 (0.4)		0 (0.0)		1 (1.2)	
Maternal alcohol consumption§							

Characteristic	Acetaminophen* (*n* = 3230)	NSAIDs* (*n* = 2518)		Opioids* (*n* = 110)		Opioids and NSAIDs* (*n* = 86)	
	n (%)	*n* (%)	*P*†	*n* (%)	*P*†	*n* (%)	*P*†
Yes	1217 (37.7)	1266 (50.3)	<.01	45 (40.9)	.35	35 (40.7)	.48
No	1958 (60.6)	1213 (48.2)		60 (54.6)		48 (55.8)	
Unknown	55 (1.7)	39 (1.6)		5 (4.6)		3 (.5)	
Maternal smoking§							
Yes	593 (18.4)	558 (22.2)	<.01	34 (30.9)	<.01	36 (41.9)	<.01
No	2585 (80.0)	1930 (76.7)		72 (65.5)		47 (54.7)	
Unknown	52 (1.6)	30 (1.2)		4 (3.6)		3 (3.5)	
Maternal use of antibiotics§							
Yes	350 (10.8)	264 (10.5)	.66	34 (30.9)	<.01	24 (27.9)	<.01
No	2844 (88.1)	2227 (88.4)		76 (69.1)		62 (72.1)	
Unknown	36 (1.1)	27 (1.1)		0 (0.0)		0 (0.0)	
Infant sex							
Male	1622 (50.2)	1280 (50.8)	.63	57 (51.8)	.74	52 (60.5)	.06
Female	1607 (49.8)	1236 (49.1)		53 (48.2)		34 (39.5)	
Unknown	1 (0.0)	2 (0.1)		0 (0.0)		0 (0.0)	
Maternal residence							
Arkansas	437 (13.5)	297 (11.8)	<.01	23 (20.9)	.38	12 (14.0)	.06
California	336 (10.4)	220 (8.7)		8 (7.3)		9 (10.5)	
Georgia	277 (8.6)	241 (9.6)		9 (8.2)		8 (9.3)	
Iowa	421 (13.0)	316 (12.6)		11 (10.0)		11 (12.8)	
Massachusetts	486 (15.1)	492 (19.5)		15 (13.6)		24 (27.9)	
New Jersey	82 (2.5)	75 (3.0)		3 (2.7)		0 (0.0)	
New York	230 (7.1)	165 (6.6)		11 (10.0)		4 (4.7)	
North Carolina	343 (10.6)	260 (10.3)		10 (9.1)		8 (9.3)	
Texas	349 (10.8)	224 (8.9)		8 (7.3)		3 (4.5)	
Utah	269 (8.3)	228 (9.1)		12 (10.9)		7 (8.1)	
Estimated date of delivery year							
1 997–2001	852 (26.4)	626 (24.9)	<.01	15 (13.6)	.01	18 (20.9)	.38
2002–2006	1269 (39.3)	890 (35.4)		46 (41.8)		33 (38.4)	
2007–2011	1109 (34.3)	1002 (39.8)		49 (44.6)		35 (40.7)	

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BMI = body mass index; NSAIDs = nonsteroidal anti-inflammatory drugs.

[*] From 1 month before conception through the third month of pregnancy; acetaminophen excluding use of NSAIDs or opioids; NSAIDs with/without acetaminophen, excluding use of opioids; opioids with/without acetaminophen, excluding use of NSAIDs; both opioids and NSAIDs with/without acetaminophen.

[†] *P* values calculated using χ^2 and Fisher's exact tests for categorical variables and two-sample *t* test for continuous variables compared to use of acetaminophen.

[‡] From 1 month before conception through the first month of pregnancy.

[§] From 1 month before conception through the third month of pregnancy.

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Table 2

Association between birth defects and maternal report of periconceptional use of NSAIDs and/or opioids compared to acetaminophen, National Birth Defects Prevention Study 1997–2011

Birth defect type (*n*)	Acetaminophen* (*n* = 11,161)	NSAIDs* (*n* = 10,378)			Opioids* (*n* = 454)			Opioids and NSAIDs* (*n* = 401)		
	n	*n*	cOR (95% CI)	aOR† (95% CI)	*n*	cOR (95% CI)	aOR† (95% CI)	*n*	cOR (95% CI)	aOR† (95% CI)
Controls (5944)	3230	2518	Referent	Referent	110	Referent	Referent	86	Referent	Referent
Gastroschisis (756)	319	401	1.6 (1.4–1.9)‡	1.6 (1.3–1.9)‡	16	1.5 (0.9–2.5)	1.4 (0.8–2.6)	20	2.4 (1.4–3.9)‡	2.3 (1.2–4.2)§
Hypospadias‖ (1384)	625	716	1.5 (1.3–1.7)‡	1.3 (1.1–1.5)‡	20	0.9 (0.5–1.5)	1.0 (0.6–1.8)	23	1.1 (0.7–1.9)	1.0 (0.6–1.6)
Orofacial clefts¶										
Cleft palate (898)	420	437	1.3 (1.1–1.5)‡	1.3 (1.1–1.5)‡	17	1.2 (0.7–2.0)	1.3 (0.7–2.2)	24	2.1 (1.3–3.4)§	2.0 (1.2–3.3)§
Cleft lip with cleft palate (1053)	495	514	1.3 (1.2–1.5)‡	1.3 (1.2–1.5)‡	25	1.5 (0.9–2.3)	1.4 (0.9–2.2)	19	1.4 (0.9–2.4)	1.4 (0.8–2.3)
Cleft lip without cleft palate (613)	301	291	1.2 (1.0–1.5)#	1.2 (1.0–1.4)#	12	1.2 (0.6–2.1)	1.1 (0.6–2.1)	9	1.1 (0.6–2.2)	0.9 (0.4–1.9)
Neural tube defects										
Anencephaly and craniorachischisis (357)	172	171	1.3 (1.0–1.6)#	1.3 (1.1–1.7)#	10	1.7 (0.9–3.3)	1.7 (0.8–3.4)	4	0.9 (0.3–2.4)	1.1 (0.4–3.1)
Encephalocele (116)	61	53	1.1 (0.8–1.6)	1.2 (0.8–1.8)	1			1		
Spina bifida (663)	298	333	1.4 (1.2–1.7)‡	1.5 (1.2–1.8)‡	15	1.5 (0.9–2.6)	1.6 (0.9–2.9)	17	2.1 (1.3–3.7)§	2.6 (1.5–4.6)‡
Heart defects										
AVSD (210)	100	99	1.3 (1.0–1.7)	1.3 (0.9–1.7)	6	1.8 (0.8–4.1)	1.9 (0.8–4.5)	5	1.9 (0.7–4.7)	2.0 (0.8–5.1)
d-TGA (414)	217	185	1.1 (0.9–1.3)	1.1 (0.9–1.4)	7	0.9 (0.4–2.1)	1.0 (0.5–2.3)	5	0.9 (0.3–2.2)	0.8 (0.3–2.0)
HLHS (325)	149	156	1.3 (1.1–1.7)#	1.4 (1.1–1.8)§	9	1.8 (0.9–3.6)	1.8 (0.9–3.8)	11	2.8 (1.4–5.3)§	2.9 (1.5–5.7)§
PVS** (849)	413	391	1.2 (1.0–1.4)#	1.3 (1.1–1.5)§	15	1.0 (0.6–1.8)	0.9 (0.5–1.7)	30	2.7 (1.7–4.1)‡	2.3 (1.5–3.7)‡
TOF (609)	282	296	1.3 (1.1–1.6)‡	1.3 (1.1–1.6)§	18	1.9 (1.1–3.1)#	2.1 (1.2–3.5)§	13	1.7 (1.0–3.1)	1.6 (0.9–3.1)
Perimembranous VSD (824)	442	351	1.0 (0.9–1.2)	1.1 (0.9–1.2)	23	1.5 (1.0–2.4)	1.8 (1.1–3.0)#	8	0.7 (0.3–1.4)	0.7 (0.3–1.5)
VSD muscular, not simple†† (342)	181	144	1.0 (0.8–1.3)	1.0 (0.8–1.3)	9	1.5 (0.7–2.9)	1.7 (0.8–3.5)	8	1.7 (0.8–3.5)	1.3 (0.5–3.0)
VSD with ASD (400)	209	169	1.0 (0.8–1.3)	1.0 (0.8–1.3)	14	2.0 (1.1–3.5)#	2.3 (1.2–4.1)§	8	1.4 (0.7–3.0)	1.1 (0.5–2.6)

aOR = adjusted odds ratio; ASD = atrial septal defect; AVSD = atrioventricular septal defect; B1 = one month before conception; CI = confidence interval; cOR = crude odds ratio; d-TGA = dextro-Transposition of the great arteries; HLHS = hypoplastic left heart syndrome; NSAIDs = nonsteroidal anti-inflammatory drugs; P9 = end of pregnancy; PVS = pulmonary valve stenosis; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

Odds ratios are presented for birth defect categories with at least four exposed cases.

[*] From one month before conception through the third month of pregnancy; acetaminophen excluding use of NSAIDs or opioids; NSAIDs with/without acetaminophen, excluding use of opioids; opioids with/without acetaminophen, excluding use of NSAIDs; both opioids and NSAIDs with/without acetaminophen.

[†] Adjusted for maternal age at delivery, race/ethnicity, parity, maternal education, periconceptional alcohol, periconceptional smoking, periconceptional antibiotic use, study location, and estimated date of delivery.

[‡] $P < .001$.

[§] $P < .01$.

[‖] Exposed controls: acetaminophen ($n = 1622$); NSAIDs only ($n = 1280$); opioids only ($n = 57$); opioids and NSAIDs ($n = 52$).

[¶] Exposed controls: acetaminophen ($n = 3179$); NSAIDs only ($n = 2501$); opioids only ($n = 109$); opioids and NSAIDs ($n = 86$).

[#] $P < .05$.

[**] Exposed controls: acetaminophen ($n = 3102$); NSAIDs only ($n = 2441$); opioids only ($n = 109$); opioids and NSAIDs ($n = 84$).

[††] Not simple denotes presence of other heart defects.

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Table 3

Association between birth defects and maternal report of periconceptional use of specific NSAIDs compared to acetaminophen, National Birth Defects Prevention Study 1997–2011

Birth defect type (*n*)	Ibuprofen* (*n* = 7299)			Aspirin* (*n* = 953)			Naproxen* (*n* = 639)		
	n	cOR (95% CI)	aOR† (95% CI)	*n*	cOR (95% CI)	aOR† (95% CI)	*n*	cOR (95% CI)	aOR† (95% CI)
Controls (5434)	1805	Referent	Referent	230	Referent	Referent	169	Referent	Referent
Gastroschisis (657)	288	1.6 (1.4–1.9)‡	1.6 (1.4–2.0)‡	34	1.5 (1.0–2.2)§	1.5 (1.0–2.4)	16	1.0 (0.6–1.6)	1.0 (0.6–1.8)
Hypospadias‖ (1240)	518	1.4 (1.3–1.7)‡	1.3 (1.1–1.5)¶	60	1.3 (0.9–1.8)	1.2 (0.9–1.7)	37	1.2 (0.8–1.8)	1.0 (0.7–1.6)
Orofacial clefts#									
Cleft palate (792)	307	1.3 (1.1–1.5)¶	1.3 (1.1–1.5)¶	40	1.3 (0.9–1.9)	1.3 (0.9–1.8)	25	1.1 (0.7–1.7)	1.1 (0.7–1.7)
Cleft lip with cleft palate (937)	361	1.3 (1.1–1.5)‡	1.3 (1.1–1.5)‡	42	1.2 (0.8–1.7)	1.1 (0.8–1.6)	39	1.5 (1.0–2.1)§	1.4 (1.0–2.1)
Cleft lip without cleft palate (556)	206	1.2 (1.0–1.5)§	1.2 (1.0–1.4)	32	1.5 (1.0–2.2)§	1.6 (1.1–2.4)§	17	1.1 (0.6–1.8)	1.1 (0.7–1.9)
Neural tube defects									
Anencephaly and craniorachischisis (316)	116	1.2 (0.9–1.5)	1.3 (1.0–1.7)§	21	1.7 (1.1–2.8)§	1.5 (0.9–2.5)	7	0.8 (0.4–1.7)	0.8 (0.4–1.7)
Encephalocele (102)	30	0.9 (0.6–1.4)	1.0 (0.6–1.5)	5	1.2 (0.5–2.9)	1.2 (0.5–3.0)	6	1.9 (0.8–4.4)	2.0 (0.9–4.9)
Spina bifida (583)	241	1.4 (1.2–1.7)‡	1.5 (1.3–1.8)‡	29	1.4 (0.9–2.0)	1.4 (0.9–2.1)	15	1.0 (0.6–1.7)	0.8 (0.4–1.4)
Heart defects									
AVSD (188)	72	1.3 (0.9–1.8)	1.3 (0.9–1.8)	11	1.5 (0.8–2.9)	1.7 (0.9–3.3)	5	1.0 (0.4–2.4)	0.9 (0.4–2.3)
d-TGA (367)	123	1.0 (0.8–1.3)	1.0 (0.8–1.3)	15	1.0 (0.6–1.7)	1.0 (0.5–1.7)	12	1.1 (0.6–1.9)	1.0 (0.6–1.9)
HLHS(281)	112	1.3 (1.0–1.7)§	1.4 (1.1–1.8)¶	14	1.3 (0.8–2.3)	1.4 (0.8–2.5)	6	0.8 (0.3–1.8)	0.8 (0.3–1.8)
PVS** (742)	281	1.2 (1.0–1.4)5§	1.3 (1.1–1.5)¶	24	0.8 (0.5–1.3)	0.9 (0.6–1.4)	24	1.1 (0.7–1.8)	1.0 (0.6–1.6)
TOF (531)	204	1.3 (1.1–1.6)¶	1.3 (1.1–1.6)¶	28	1.4 (0.9–2.1)	1.3 (0.8–2.0)	17	1.2 (0.7–1.9)	1.0 (0.6–1.7)
Perimembranous VSD (739)	236	1.0 (0.8–1.1)	1.1 (0.9–1.3)	40	1.3 (0.9–1.8)	1.2 (0.8–1.7)	21	0.9 (0.6–1.4)	0.7 (0.4–1.2)
VSD muscular, not simple†† (310)	105	1.0 (0.8–1.3)	1.1 (0.8–1.4)	14	1.1 (0.6–1.9)	0.9 (0.5–1.7)	10	1.1 (0.5–2.0)	0.9 (0.5–1.9)
VSD with ASD (356)	109	0.9 (0.7–1.2)	1.0 (0.8–1.2)	25	1.7 (1.1–2.6)§	1.6 (1.0–2.5)	13	1.2 (0.7–2.1)	1.0 (0.6–1.9)

aOR = adjusted odds ratio; ASD = atrial septal defect; AVSD = atrioventricular septal defect; B1 = one month before conception; CI = confidence interval; cOR = crude odds ratio; d-TGA = dextro-Transposition of the great arteries; HLHS = hypoplastic left heart syndrome; NSAIDs = nonsteroidal anti-inflammatory drugs; P9 = end of pregnancy; PVS = pulmonary valve stenosis; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

Odds ratios are presented for birth defect categories with at least four exposed cases.

[*] From 1 month before conception through third month of pregnancy.

[†] Adjusted for maternal age at delivery, race/ethnicity, parity, maternal education, periconceptional alcohol, periconceptional smoking, periconceptional antibiotic use, study location, and estimated date of delivery.

[‡] $P < .001$.

[§] $P < .05$.

[‖] Exposed controls: ibuprofen ($n = 931$); aspirin ($n = 121$); naproxen ($n = 80$).

[¶] $P < .01$.

[#] Exposed controls: ibuprofen ($n = 1791$); aspirin ($n = 229$); naproxen ($n = 169$).

[**] Exposed controls: ibuprofen ($n = 1760$); aspirin ($n = 218$); naproxen ($n = 160$).

[††] Not simple denotes presence of other heart defects.

Table 4

Association between birth defects and maternal report of periconceptional use of specific opioids compared to acetaminophen, National Birth Defects Prevention Study 1997–2011

Birth defect type (*n*)	Hydrocodone* (*n* = 152)			Codeine* (*n* = 131)		
	n	cOR (95% Cl)	aOR† (95% CI)	*n*	cOR (95% CI)	aOR† (95% CI)
Controls (3305)	29	Referent	Referent	30	Referent	Referent
Gastroschisis (332)	8	2.8 (1.3–6.2)‡	2.0 (0.8–5.0)	2		
Hypospadias§ (640)	5	1.0 (0.4–2.8)	1.3 (0.4–4.3)	8	1.1 (0.5–2.5)	1.2 (0.5–2.8)
Orofacial clefts‖						
Cleft palate (434)	10	2.7 (1.3–5.6)¶	2.9 (1.3–6.4)¶	4	1.0 (0.4–2.9)	1.2 (0.4–3.3)
Cleft lip with cleft palate (517)	13	3.0 (1.5–5.8)¶	2.8 (1.4–5.5)¶	5	1.1 (0.4–2.8)	0.8 (0.3–2.4)
Cleft lip without cleft palate (310)	5	1.9 (0.7–4.9)	1.6 (0.6–4.2)	4	1.4 (0.5–4.0)	1.4 (0.5–4.2)
Neural tube defects						
Anencephaly and craniorachischisis (181)	5	3.2 (1.2–8.5)‡	2.3 (0.8–7.0)	4	2.5 (0.9–7.2)	2.5 (0.8–7.6)
Encephalocele (62)	1			0		
Spina bifida (308)	3			5	1.8 (0.7–4.7)	2.0 (0.7–5.2)
Heart defects						
AVSD (104)	1			3		
d-TGA (222)	1			3		
HLHS (155)	3			3		
PVS# (427)	6	1.6 (0.7–3.9)	1.1 (0.4–3.3)	4	1.0 (0.4–2.9)	1.1 (0.4–3.1)
TOF (296)	8	3.2 (1.4–7.0)¶	3.7 (1.6–8.5)¶	2		
Perimembranous VSD (460)	8	2.0 (0.9–4.4)	2.5 (1.1–5.9)‡	8	1.9 (0.9–4.3)	2.7 (1.2–6.1)‡
VSD muscular, not simple ** (186)	2			2		
VSD and ASD (217)	4	2.1 (0.7–6.1)	2.7 (0.9–8.2)	3		

aOR = adjusted odds ratio; ASD = atrial septal defect; AVSD = atrioventricular septal defect; B1 = one month before conception; CI = confidence interval; cOR = crude odds ratio; d-TGA = dextro-Transposition of the great arteries; HLHS = hypoplastic left heart syndrome; NSAIDs = nonsteroidal anti-inflammatory drugs; P9 = end of pregnancy; PVS = pulmonary valve stenosis; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

Odds ratios are presented for birth defect categories with at least four exposed cases.

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[*] From 1 month before conception through third month of pregnancy.

[†] Adjusted for maternal age at delivery, race/ethnicity, parity, maternal education, periconceptional alcohol, periconceptional smoking, periconceptional antibiotic use, study location, and estimated date of delivery.

[‡] $P < .05$.

[§] Exposed controls: hydrocodone ($n = 13$); codeine ($n = 19$).

[‖] Exposed controls: hydrocodone ($n = 28$); codeine ($n = 30$).

[¶] $P < .01$.

[#] Exposed controls: hydrocodone ($n = 28$); codeine ($n = 30$).

[**] Not simple denotes presence of other heart defects.